S/N 09/730374 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	John A. Lust et al.	Examiner: A. S. Wehbé
Serial No.:	09/730374	Group Art Unit: 1632
Filed:	December 5, 2000	Docket No.: 150.188US2
Title:	USE OF GENETICALLY ENGINEERED ANTIBODIES TO CD38 TO TREAT MULTIPLE MYELOMA	

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, John A. Lust, M.D., Ph.D., declare and say as follows:

1. I am a coinventor of subject matter claimed in the above-identified application, and I make this Declaration in support of the patentability of the claims in the application, as amended by the Amendment which accompanies this Declaration.

2. In the Office Action mailed on November 7, 2002 for the present application, the Examiner rejected claims 1-13, 15 and 18 under 35 U.S.C. ' 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Examiner asserts that the specification fails to provide an enabling disclosure for targeting $CD38^+$ cells, including multiple myeloma cells *in vivo*, using a fusion polypeptide comprising an anti-CD38 antibody or complexed *in vitro* with plasmid DNA, and that the *in vivo* use of immunotoxins as of the effective date of the application was unpredictable due to their immunogenicity, toxicity, and lack of specificity.

3. In addition to the data described in the specification, my laboratory has shown that complexes of a fusion polypeptide comprising an anti-CD38 antibody and a DNA binding protein and plasmid DNA, bound to $CD38^+$ cells. Specifically, flow cytometric analysis demonstrated target specific binding of an anti-CD38 scFv-protamine protein to $CD38^+$ myeloma cells. To determine whether complexes of the anti-CD38 scFv-protamine and a plasmid are internalized, complexes of the anti-CD38 scFv-

protamine and a β-galactosidase encoding plasmid were incubated with $CD38^+$ 8226 human myeloma cells for 48 hours at 37^0C. Positive blue cells were identified among the 8226 cells incubated with the complexes but not when 8226 cells were incubated with anti-CD38 scFv-protamine alone or with β-gal plasmid alone.

Therefore, $CD38^+$ cells were targeted with a complex of a fusion polypeptide comprising an anti-CD38 antibody and a DNA binding protein and a plasmid, and the plasmid was internalized and expressed in the targeted cells. Further, these *in vitro* results are reasonably predictive of *in vivo* results, e.g., reasonably predictive that the complexes would bind to and be internalized by $CD38^+$ cells *in vivo*. For example, in Maloney et al. (Sem. in Hematol., 36:30 (1999)), a reference cited in the Office Action, four patients were treated with anti-CD38 antibodies and one of the four responded with a reduction in marrow plasma cells and M-protein.

4. Moreover, the predictability of immunotherapy for lymphoma has been shown using Rituxan, an anti-CD20 antibody-based therapy, and is also exemplified for anti-CD38 antibodies in Maloney et al. Although the study in Maloney et al. was not even a Phase I trial, a positive result was observed in one of four patients treated with anti-CD38 antibodies. As for the three other patients, it is likely that they did not receive an adequate dose of anti-CD38 antibodies to achieve the same effect. Further, in contrast to CD20 bound by Rituxan, CD38 bound by anti-CD38 antibodies is rapidly internalized from the surface of myeloma cells, which is an advantage of the present invention for treating disorders of $CD38^+$ cells.

5. In fact, the use of antibodies is recognized as one, if not the best, current approach for targeting *in vivo*. Moreover, parameters for the *in vivo* administration of antibodies are reasonably well developed, as evidenced by the therapeutic use of agents such as Rituxan.

6. Thus, in view of the recognized targeting achieved by antibodies *in vivo*, the present specification enables the preparation and *in vivo* use of complexes of a fusion polypeptide comprising an anti-CD38 antibody and a DNA binding protein and a plasmid.

7. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and

further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 2/6/03 By: John A. Lust

John A. Lust, M.D., Ph.D.

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Washington, D.C. 20231

Sir:

I, Anne Koch, declare and say as follows:

1. I am in the employ of Schwegman, Lundberg, Woessner & Kluth, P.A., 1600 TCF Tower, 121 South Eighth Street, Minneapolis, Minnesota 55402, Applicant's attorney of record in the above-identified patent application.

2. On January 21, 2003, I was informed by a representative of Blood that Volume 90 of Blood in which the Donovan et al. abstract entitled "Binding and internalization of an antibody engineered anti-CD38 single chain variable fragment (scFv) by human myeloma cells" appears, was not available to the public earlier than November 1997.

3. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 2-6-03

By: Anne Koch
Anne Koch